

**REMARKS**

Independent claim 21 has been amended to clarify the invention. No new matter has been entered.

All of the claims have been rejected as being anticipated by EP '252. Claims 35-40 also have been rejected under 35 USC § 112, first paragraph. As will be discussed below in detail, both of these rejections are in error.

Considering first the 102 rejection, it is hornbook law that disclosures in a reference relied on to prove anticipation must be so clear and explicit that those skilled in the art will have no difficulty in ascertaining their meaning. In re Turlay, 304 F.2d 893, 899; 134 USPQ 355, 360 (CCPA 1962). It is submitted that EP '252 fails to provide the requisite clear and explicit teaching of Applicants' claims. EP'252 discloses the beneficial effect of inulin and/or oligofructose against breast cancer, in particular the use of inulin and/or oligofructose for the manufacture of a medicament (= pharmaceutical composition) for the prevention of mammary carcino-genesis and/or the treatment of breast cancer (EP'252, p.2, lines 49-57 and claims 1 to 5).

EP'252 also discloses that said pharmaceutical composition may furthermore comprise conventional chemotherapeutic products that actively destroy malignant tumour cells (EP'252, p.3, lines 5-6 and claim 6). A listing of the various classes of conventional chemotherapeutic products that actively destroy malignant tumour cells, together with an enumeration of typical examples of these chemotherapeutic products, are given in EP'252 on p.3, lines 6-20 (source: Répertoire commenté des médicaments, Centre Belge d'information pharmacothérapeutique, 1987, excerpt p.341-345 [copy enclosed herewith]).

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Applicants submit that at best the disclosure of EP'252 about pharmaceutical compositions containing inulin and/or oligofructose that furthermore comprise a conventional chemotherapeutic product is merely a generic, vague, non-enabling disclosure in view of the subject invention.

Indeed, in EP'252 there are no specific pharmaceutical compositions described containing a combination of inulin and/or oligofructose and a conventional chemotherapeutic product disclosed, apart from Example 7 (EP'252, p.10, lines 41-47). However, even Example 7 is a vague and indefinite disclosure because Example 7 in fact only discloses an aim ("to determine a synergistic therapeutic effect"), and there are no experimental results disclosed. Example 7 is thus silent about the existence of a possible synergistic therapeutic effect against breast cancer of a composition containing a combination of inulin/oligofructose and a conventional chemotherapeutic product.

Besides, Applicants emphasise that Example 7 relates to a pharmaceutical composition that contains Raftiline® (= chicory inulin) and a doxorubicine derivative, a chemo-therapeutic product that belongs to the class of antimitotic antibiotics, whereas the subject invention relates to combinations of inulin and a chemotherapeutic product that belongs to the class of the antimetabolites (see the listing given on p.3, lines 6-20 of EP'252, as well as p. 343 (whole page) and. p.344 (under ADRIBLASTINA) of the "Répertoire commenté des médicaments, Centre Belge d'information pharmacothérapeutique, 1987).

Thus, doxorubicine (an antimitotic antibiotic) and antimetabolites clearly belong to different classes of chemotherapeutic products, and it is common knowledge of one skilled in the art that there is an essential difference between both classes of chemotherapeutic products

with respect to the mode of action (antimetabolites interfere with the synthesis of nucleic acids, whereas doxorubicine presents potent antimitotic effects).

Besides, the results of the comparative tests presented in Table 1 and Table 2 of the subject patent application (p.14 and p.15) evidence the criticality of the particular combination between inulin and an antimetabolite chemotherapeutic product for obtaining a synergistic anticancer effect. Indeed, from the experimental data disclosed in Tables 1 and 2 regarding the combinations of inulin with chemotherapeutic products belonging to different classes, it clearly follows that only the claimed combination of inulin with an antimetabolite presents synergistic anticancer effects (see also Amendment C, p.11, last § to p.12, §2). The findings that said particular combination of inulin and an antimetabolite product provides a synergistic anticancer effect were clearly unexpected for the person skilled in the art.

Having regard to the above, Applicants state that the subject matter of the present patent application cannot be directly and non-ambiguously derived from Example 7 of EP'252, nor from any other disclosure of EP'252. Accordingly, Example 7 is at best ambiguous, and one skilled in the art would be inclined to interpret the absence of experimental results in Example 7 as a strong indication that no synergistic effects were observed. The Board of Appeals has stated "It is well established that an anticipation rejection cannot be predicated on an ambiguous reference" (See unpublished opinion in Appeal No. 2002-1731, citing In re Turley).

Accordingly, the subject matter of claims 21-33 and claims 35-42 has to be considered novel and not anticipated by EP'252, because EP '262 does not exactly and unambiguously teach disclose every element of what is claimed in the claims of the subject patent application. Therefore, Applicants respectfully submit that the rejection of pending claims 21-33 and claims

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35-42 is in error, and submit that the claimed subject matter is in compliance with the requirements of 35 USC 102(b), and the continued rejection of the claims as anticipated by EP '262 is in error.

Turning to the rejection of the claims under 35 USC § 112, first paragraph, it is noted only claims 35-40 have been so rejected. Applicants submit that this rejection likewise is in error.

As pointed out by the Board of Appeals in its decision in Appeal No. 1996-3409, "It is well settled that the examiner bears the initial burden of providing reasons why a supporting disclosure does not enable a claim." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In the instant case, the Examiner's principal position is that undue experimentation would be required to practice the claimed invention because "the specification, while being enabling for the treatment of certain cancers, does not reasonably provide enablement for "the treatment of cancer" in general". The Examiner also is concerned with the "considerable amount of invitro empirical testing [is] required with no prior expectation of success being present, before a candidate anti-cancer agent can be considered useful against any particular cancer type". (See pages 2 and 4 of the Action).

While Applicants' claims admittedly are broad, they are not overly broad. All of Applicants' claims specify a particular material inulin, and a particular type of anti-cancer drug, namely, an anti-metabolic anti-cancer drug. Both of these products that are well known. Applicant is not claiming to have invented a new anti-metabolic anti-cancer drug candidate. Rather, Applicants' claims are all directed to the synergistic combination of inulin and an anti-metabolic anti-cancer drug. Since the anti-metabolic anti-cancer drugs already would have undergone invitro empirical testing, the only additional testing required would be to test a

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combination of inulin and a known anti-metabolic anti-cancer candidate drug, i.e., to determine if there is a synergistic effect from the combination. As stated in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The Patent and Trademark Office Board of Appeals summarized this point in Ex parte Jackson, 217 USPQ 804, 807 (1982):

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentations should proceed to enable the determination of how to practice a desired embodiment of the invention.

Moreover, it is well settled that the specification need not disclose what is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986).

Here, the Examiner has not presented any evidence that one skilled in the art would be unable to identify anti-metabolic anti-cancer drugs. Thus, the rejection of claims 35-40 under 35 USC § 112, first paragraph is in error.

Moreover, though cancer is commonly known as a disease that can appear under the form of several kinds (types) of cancer, cancer is also known to be a disease that arises and proceeds according to a mechanism that is similar for the various kinds of cancer (see e.g. description, p.1, lines 15-31).

Accordingly, an anticancer drug belonging to one class of chemotherapeutic compounds (which by definition interferes with a certain step of the genesis or progression of the cancer

[see Description, p.2, lines 18-28]], generally presents anti-cancer effects against a wide range of kinds of cancer (since all these kinds of cancer arise and proceed through a same or very similar mechanism). This consequently also applies to the class of antimetabolites

Support for the above is provided by the enclosed information obtained from Medline Plus® for several typical antimetabolites that are mentioned in the listing of the chemotherapeutic products “Répertoire commenté des médicaments, Centre Belge d’information pharmacothérapeutique, 1987, p.341-345 ”, for example fluorouracil, methotrexate, cytarabine, mercaptopurine, thioguanine and hydroxycarbamide (see the excerpts from Medline Plus® Drug information and the summary thereof, given in Table 1, enclosed herewith).

Having regard to the above, Applicants submit that the subject matter of claims 35-40 reading broadly on “cancer” finds adequate support in the fact that the antimetabolite anticancer drugs, the effects of which are synergistically enhanced in the compositions according to the subject invention, are known to one skilled in the art to present an anti-cancer activity against a wide range of cancers.

Furthermore, Applicants respectfully submit that when considering the treatment of a particular kind of cancer by a method involving a pharmaceutical composition defined in any of claims 21 to 33 and claims 41-42 by a method defined in any of claims 35 to 40 according to the subject invention, one skilled in the art would not be confronted with an undue burden to define the particulars of the composition and/or the method of treatment to be used for a given antimetabolite and/or a given kind of cancer. Indeed, the required information is readily available from the prior art for each antimetabolite and each kind of cancer, while the person

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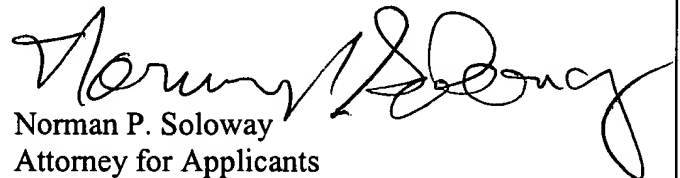
skilled in the art easily can determine whether the anti-cancer effect of said antimetabolite is enhanced by its combination with inulin in accordance with the subject invention.

Accordingly, Applicants submit that the claimed subject matter has been disclosed in an enabling manner in compliance with the requirements of 35 USC 112 §1.

Having dealt with all the objections raised by the Examiner, the Application is believed to be in order for allowance. Early and favorable action are respectfully requested.

In the event there are any fee deficiencies or additional fees are payable, please charge them (or credit any overpayment) to our Deposit Account Number 08-1391.

Respectfully submitted,



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# **REPertoire COMMENTE DES MEDICAMENTS**

**1987**

**CENTRE BELGE  
D'INFORMATION PHARMACOTHERAPEUTIQUE**

## ANTITUMORAUX

Ce chapitre reprend successivement:

- les agents alkylants
- les antimétabolites
- les antibiotiques antimitotiques
- les alcaloïdes antitumoraux
- divers antitumoraux.

Les hormones ou antihormones utilisées notamment dans les cancers du sein, des organes génitaux féminins et de la prostate sont reprises avec les médicaments du système hormonal.

Les médicaments antitumoraux sont responsables d'effets toxiques dont la gravité peut détériorer la qualité de la survie. Ceux-ci doivent être décelés aussi précocement que possible. La dépression de la moelle osseuse favorise des infections graves et provoque des hémorragies par thrombopénie; des contrôles hématologiques réguliers sont donc nécessaires. La destruction des cellules néoplasiques peut entraîner une hyperuricémie que l'allopurinol permet éventuellement de corriger. L'action irritante habituelle de ces substances sur les muqueuses digestives est souvent à l'origine de nausées, de vomissements et de diarrhée même lors d'administration parentérale. L'alopécie est d'apparition fréquente. La chimiothérapie est dangereuse pour l'embryon; au cours du traitement une méthode de contraception efficace sera préconisée chez les femmes en âge de procréer. Une atteinte de la fonction ovarienne ou de la spermatogenèse, avec risque de stérilité chez l'homme, est souvent observée spécialement avec les agents alkylants.

Plusieurs de ces médicaments sont très irritants localement et peuvent provoquer des nécroses lors d'injection paraveineuse accidentelle.

Les effets indésirables particuliers à chaque groupe ou à chacun de ces médicaments sont mentionnés aux rubriques respectives.

Les médicaments antitumoraux sont délicats à manier et leur emploi requiert de l'expérience. Les options thérapeutiques relèvent du spécialiste. Les indications, la posologie et le mode d'emploi de ces médicaments (solvants, mode de préparation précis des solutions) ne sont donc pas repris ici.

Pour les spécialités à usage hospitalier (U.H.) seul le plus petit conditionnement a été repris.

### 1. Agents alkylants

Ces substances possèdent des groupements alkyles hautement réactifs qui se lient à certaines biomolécules et en particulier à l'ADN. Elles inhibent ainsi la multiplication cellulaire, principalement dans les tissus à activité mitotique élevée.

Selon leur structure chimique, on les divise en dérivés de l'ypérite (moutardes à l'azote): chlorambucil, chlorméthine, cyclophosphamide et melphalan, en nitroso-urées: carmustine et

lomustine, et autres dérivés appartenant à des classes chimiques variées: busulfan, cisplatine et thiotépa.

Ces médicaments peuvent provoquer une atteinte de la fonction ovarienne et de la spermatogénèse ainsi qu'une fibrose pulmonaire; ils sont tératogènes et cancérogènes.

**ALKERAN (Wellcome)**

melphalan  
compr. 25 x 2 mg R/ 347 F (a)  
flacon i.v. - in situ  
1 x 100 mg poudre  
+ 9 ml solv. R/ 952 F (a)

**CECENU (Rhône-Poulenc)**

lomustine  
caps. 50 x 40 mg U.H.

**CYCLOBLASTINE (Farmitalia Carlo Erba)**

cyclophosphamide  
drag. 50 x 50 mg R/ 247 F (a)  
flacon i.v.  
10 x 100 mg poudre R/ 385 F (a)  
10 x 200 mg poudre R/ 529 F (a)  
10 x 500 mg poudre R/ 1041 F (a)  
1 x 1 g poudre R/ 267 F (a)  
(cystite hémorragique; aussi utilisé comme immunosuppresseur,  
autre marque déposée: Endoxan)

**ENDOXAN (Asta Werke/Cilag)**

cyclophosphamide  
drag. 50 x 50 mg R/ 247 F (a)  
flacon i.v. (i.m. éventuellement)  
10 x 100 mg poudre R/ 385 F (a)  
10 x 200 mg poudre R/ 529 F (a)  
flacon i.v. 5 x 500 mg poudre R/ 575 F (a)  
(cystite hémorragique, aussi utilisé comme immunosuppresseur  
autre marque déposée: Cycloblastine)

**ESTRACYT (Leo/Bios-Coutelier)**

estramustine phosphate  
caps. 40 x 140 mg R/ 3490 F (a)  
100 x 140 mg R/ 7300 F (a)  
flacon i.v. 10 x 300 mg + 8 ml solv. R/ 4227 F (a)  
(gynécomastie, rétention hydrique)

**LEDERTEPA (Lederle/Cyanamid)**

thiotépa  
flacon i.m. - i.v. - in situ  
1 x 15 mg poudre R/ 157 F (a)  
(autre marque déposée: Oncotitepa)

**LEUKERAN (Wellcome)**

chlorambucil  
drag. 25 x 5 mg R/ 413 F (a)  
(aménorrhée, azoospermie)

**MUSTINE CHLORH. B.P. (Boots)**

chlorméthine chlorhydrate  
flacon i.v. 10 mg poudre U.H.  
(symptômes cholinergiques: diarrhée, myosis,  
vomissements, nécrose tissulaire en cas d'ex-  
travasation)

**MYLERAN (Wellcome)**

busulfan  
compr. 100 x 2 mg R/ 638 F (a)  
(gynécomastie, éruption cutanée, hyperpigmen-  
tation)

**NITRUMON (Sintesa)**

carmustine  
flacon i.v. 1 x 100 mg poudre R/ 953 F (a)  
(toxicité hépatique et rénale, vertiges, perte  
d'équilibre, ataxie)

**ONCOTITEPA (Sintesa)**

thiotépa  
amp. i.m. - i.v. - intra-artériel - in situ  
5 x 10 mg + 5 x 4 ml solv. R/ 176 F (a)  
(autre marque déposée: Ledertepa)

**PLATINOL (Bristol)**

cisplatine  
flacon i.v. 10 mg/ 20 ml U.H.  
25 mg/ 50 ml U.H.  
50 mg/100 ml U.H.  
flacon i.v. 50 mg poudre U.H.  
(toxicité rénale, ototoxicité, neurotoxicité, réac-  
tions de type anaphylactique  
autre marque déposée: Platistine)

**PLATISTINE (Farmitalia Carlo Erba)**

cisplatine  
flacon i.v. 10 mg poudre U.H.  
25 mg poudre U.H.  
50 mg poudre U.H.  
(toxicité rénale, ototoxicité, neurotoxicité, réac-  
tions de type anaphylactique  
autre marque déposée: Platinol)

**2. Antin**

Les anti  
synthèse  
cytostati  
l'acide fo  
ne, fluo  
presseur  
de psori  
de ce mé  
sous forr

Les antin  
ils peue  
ulcération  
de fibros

**ALEXAN (I**

cytarat  
amp. i.  
10 x  
30 x  
10 x  
1 x  
(convu  
autre m

**CYTOSAR**

cytarat  
flacon i  
1 x

1 x

(convul  
autre m

**EMTHEXA**

méthot  
flacon i

(remarc  
autre m

**FLUORO-L**

fluorou  
amp. i.v.  
(neuroto  
hyperpi

**HYDREA (S**

hydroxy  
caps. 20

cisplatine

dermatog-

**2. Antimétabolites**

Les antimétabolites entrent en compétition avec des métabolites normaux de la chaîne de synthèse cellulaire des acides nucléiques. Ils sont souvent utilisés en même temps que d'autres cytostatiques. Parmi les antimétabolites actuellement disponibles, on trouve un antagoniste de l'acide folique (méthotrexate), des antagonistes des bases pyrimidiniques ou puriques (cytarabine, fluorouracile, mercaptopurine, tioguanine), l'azathioprine (décrite au chapitre Immunosuppresseurs) et enfin l'hydroxycarbamide. Le méthotrexate est de plus utilisé dans des cas graves de psoriasis mais il s'agit là d'une thérapeutique d'exception en raison des effets indésirables de ce médicament. Le fluorouracile est également utilisé dans des kératoses et tumeurs cutanées sous forme de préparations locales (v. chapitre Préparations à usage dermatologique).

Les antimétabolites présentent les effets indésirables communs à tous les cytostatiques. En outre, ils peuvent causer une mégalo-blastose, des lésions du foie et du tube digestif (stomatites, ulcérations buccales et parfois gastro-intestinales). Le méthotrexate peut aussi être responsable de fibrose pulmonaire, d'ostéoporose, de toxicité rénale et d'éruptions cutanées.

**ALEXAN (Mack/de Boumonville)**

cytarabine  
amp. i.m. - i.v. - intra-rach - s.c.  
10 x 40 mg/ 2 ml R/ 1056 F (a)  
30 x 40 mg/ 2 ml R/ 2888 F (a)  
10 x 100 mg/ 5 ml R/ 1662 F (a)  
1 x 500 mg/25 ml R/ 1003 F (a)  
(convulsions  
autre marque déposée: Cytosar)

**CYTOSAR (Upjohn)**

cytarabine  
flacon i.v.  
1 x 100 mg poudre  
+ 5 ml solv. R/ 275 F (a)  
1 x 500 mg poudre  
+ 10 ml solv. R/ 1003 F (a)  
(convulsions  
autre marque déposée: Alexan)

**EMTHEXATE (Conforma)**

méthotrexate  
flacon i.v. 1 x 5 mg poudre R/ 139 F (a)  
1 x 50 mg poudre U.H.  
1 x 500 mg poudre U.H.  
1 x 1 g poudre U.H.  
(remarque: voir Ledertrexate SP  
autre marque déposée: Ledertrexate)

**FLUORO-URACIL (Roche)**

fluorouracile  
amp. i.v. 5 x 250 mg/10 ml R/ 623 F (a)  
(neurotoxicité, ataxie cérébelleuse,  
hyperpigmentation, photosensibilisation)

**HYDREA (Squibb)**

hydroxycarbamide  
caps. 20 x 500 mg R/ 330 F (a)

**LANVIS (Wellcome)**

tioguanine  
compr. séc. 25 x 40 mg R/ 1154 F (a)

**LEDERTREXATE (Lederle/Cyanamid)**

méthotrexate  
compr. 100 x 2,5 mg R/ 665 F (a)  
(remarque: voir Ledertrexate SP  
autre marque déposée: Emthexate)

**LEDERTREXATE SODIUM (Lederle/Cyanamid)**

méthotrexate  
flacon i.m. - i.v. - intra-artériel  
12 x 5 mg poudre R/ 1348 F (a)  
1 x 50 mg poudre U.H.  
1 x 500 mg poudre U.H.  
(remarque: voir Ledertrexate SP  
autre marque déposée: Emthexate)

**LEDERTREXATE SP (Lederle/Cyanamid)**

méthotrexate  
amp. intrathécale  
1 x 5 mg/2 ml R/ 177 F (a)  
1 x 50 mg/2 ml U.H.  
(SP: sans agent conservateur;  
par voie intrathécale: méningisme et convulsions, rarement encéphalite nécrosante;  
l'acide folinique (LEDERVORIN Ca<sup>2+</sup> - chapitre Vitamines) est souvent associé au traitement par méthotrexate comme antidote)

**PURI-NETHOL (Wellcome)**

mercaptopurine  
compr. 25 x 50 mg R/ 545 F (a)  
(doses à réduire en cas d'administration concomitante d'allopurinol)

U.H.  
ne, myosis,  
cas d'ex-638 F (a)  
hyperpigmen-953 F (a)  
ges, perte

176 F (a)

U.H.  
U.H.  
U.H.  
U.H.  
toxicité, réac-U.H.  
U.H.  
U.H.  
toxicité, réac-

### 3. Antibiotiques antimitotiques

Plusieurs antibiotiques produits par différentes souches de streptomyces et trop toxiques pour être utilisés comme antibactériens sont doués de propriétés antitumorales.

La mithramycine est également utilisée dans des hypercalcémies d'origine maligne ou pagétique.

Toutes ces substances présentent les effets indésirables des autres cytostatiques sauf la bléomycine qui n'a pas de toxicité hématologique; il existe aussi une cardiotoxicité.

#### ADIRIBLASTINA (Farmitalia Carlo Erba)

doxorubicine  
flacon i.v. 1 x 10 mg poudre  
+ 5 ml solv. R/ 1034 F (a)  
5 x 10 mg poudre  
+ 5 ml solv. R/ 3695 F (a)  
1 x 50 mg poudre + solv. U.H.  
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

#### BLEOMYCINE (Bellon/Wellcome)

bléomycine  
flacon i.m. - i.v. - intra-artériel - in situ  
1 x 15 mg poudre R/ 1234 F (a)  
(fibrose pulmonaire, éruptions cutanées, stomatite, hyperpigmentation, sclérose digitale, syndrome de Raynaud)

#### CERUBIDINE (Rhône-Poulenc)

daunorubicine  
flacon i.v. 1 x 20 mg poudre  
+ 4 ml solv. R/ 549 F (a)  
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

### 4. Alcaloïdes antitumoraux

Ces substances bloquent la mitose en métaphase. Trois alcaloïdes de la pervenche sont utilisés en clinique: la vinblastine, la vincristine et la vindésine. En plus des effets indésirables habituels des cytostatiques (mise à part la dépression médullaire qui est plus rare) ils peuvent être responsables d'asthénie, de troubles visuels, de constipation et parfois d'iléus paralytique ainsi que de polyneuropathie. Cette toxicité neurologique s'observe surtout avec la vincristine. Une sécrétion inappropriée d'hormone antidiurétique a également été signalée.

#### ELDISINE (Eli Lilly)

vindésine sulfate  
flacon i.v. 1 x 1 mg poudre R/ 1512 F (a)  
1 x 5 mg poudre R/ 4558 F (a)

#### FARMORUBICINE (Farmitalia Carlo Erba)

épirubicine chlorhydrate  
flacon i.v. 10 mg poudre R/ 1137 F (a)  
50 mg poudre R/ 4317 F (a)  
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

#### LYOVAC COSMEGEN (M.S.D.)

dactinomycine  
flacon i.v.  
1 x 0,5 mg poudre R/ 145 F (a)  
(réactions locales et phlébites, ulcérations digestives, érythème, hyperpigmentation, acné)

#### MITOMYCINE (Christiaens)

mitomycine c  
flacon i.v. - intra-artériel  
10 x 2 mg poudre R/ 2647 F (a)  
3 x 10 mg poeder R/ 3625 F (a)  
(réactions locales, stomatite, nécrose tissulaire en cas d'extravasation)

#### NOVANTHRONE (Lederle/Cyanamid)

mitoxantrone  
flacon i.v. 20 mg/10 ml R/ 8988 F (a)  
25 mg/12,5 ml R/ 11150 F (a)

#### ONCOVIA

vincristine  
flacon

### 5. Interf.

L'interférer  
s'accompagne  
confusion

#### INTRONA

alfa-2  
flacon

### 6. Antitu

L'étopos  
effets inc

L'aminog  
syndrom

L'amsaci  
leucémie  
ments.

#### AMSIDINE

amsac  
flacon  
+ 1%

#### DTIC-DOX

dacart  
flacon  
12 x  
(syndr  
parest  
te d'inj

#### NATULAN

procar  
caps. 1  
(dépre  
pathie  
mine o  
matite)

**ONCOVIN (Eli Lilly)**

vincristine sulfate	
flacon i.v. 1 × 1 mg poudre	
+ 10 ml solv.	R/ 837 F (a)
1 × 2 mg poudre	
+ 10 ml solv.	R/ 1248 F (a)
1 × 5 mg poudre	
+ 10 ml solv.	R/ 2923 F (a)

**VELBE (Eli Lilly)**

vinblastine sulfate	
flacon i.v. 1 × 10 mg poudre	R/ 896 F (a)
(stomatite)	

**5. Interféron**

L'interféron  $\alpha_2$  b peut être utilisé en cas d'affections hématologiques malignes et de maladies s'accompagnant de déficience immunitaire. Une dépression du système nerveux central, de la confusion, des éruptions cutanées, une stomatite et des troubles de la coagulation ont été décrits.

**INTRON A (Schering Corp. Essex)**

alfa-2 b interféron	
flacon s.c. - inf. 3 × 10 <sup>6</sup> UI	R/ 1753 F
5 × 10 <sup>6</sup> UI	R/ 2590 F
10 × 10 <sup>6</sup> UI	R/ 4682 F
30 × 10 <sup>6</sup> UI	R/ 13 053 F

**6. Antitumoraux divers**

L'étoposide et le téniposide sont des dérivés semi-synthétiques de la podophyllotoxine. Leurs effets indésirables sont ceux des cytostatiques en général.

L'aminoglutéthimide est utilisé dans les tumeurs du sein hormono-dépendantes et dans le syndrome de Cushing.

L'amsacrine est un dérivé synthétique de l'acridine. Elle est utilisée dans le traitement des leucémies aiguës non lymphoblastiques qui n'ont pas répondu favorablement à d'autres traitements.

**AMSIDINE (Parke-Davis)**

amsacrine	
flacon perf. 5 × 75 mg/1,5 ml	
+ 13,5 ml solv.	U.H.

**ORIMETEN (Ciba-Geigy)**

aminoglutéthimide	
compr. séc. 100 × 250 mg	R/ 2258 F (b)

**DTIC-DOME (Miles/Frère)**

dacarbazine	
flacon i.v.	
12 × 100 mg poudre	R/ 2671 F (a)
(syndrome pseudogrippal, atteinte hépatique, paresthésies, éruptions cutanées, douleur au site d'injection)	

**VEPESID (Bristol)**

étoposide	
caps. 10 × 100 mg	R/ 4221 F (a)
amp. perf. 10 × 100 mg/5 ml	R/ 5118 F (a)

**NATULAN (Roche)**

procarbazine	
caps. 50 × 50 mg	R/ 224 F (a)
(dépression du système nerveux central, neuropathie périphérique, effet inhibiteur des monoamine oxydases, effet disulfiram, stomatite, dermatite)	

**VUMON (Bristol)**

téniposide	
amp. perf. 10 × 50 mg/5 ml	R/ 2088 F (a)

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## Drug Information: Fluorouracil (Systemic)

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202245.html>

### Brand Names

#### In the U.S.—

- Adrucil

#### In Canada—

- Adrucil

Another commonly used name is 5-FU.

### Category

- Antineoplastic

### Description

Fluorouracil ( flure-oh-YOOR-a-sill) belongs to the group of medicines known as antimetabolites. It is used to treat cancer of the colon, rectum, breast, stomach, and pancreas. It may also be used to treat other kinds of cancer, as determined by your doctor.

Fluorouracil interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by fluorouracil, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with fluorouracil, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Fluorouracil is to be administered only by or under the immediate supervision of your doctor. It is available in the following dosage form:

#### *Parenteral*

- Injection (U.S. and Canada)

### Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

Check with your doctor or nurse immediately if any of the following side effects occur:

- **More common**
  - Diarrhea; heartburn; sores in mouth and on lips
- **Less common**
  - Black, tarry stools; cough or hoarseness, accompanied by fever or chills; fever or chills; lower back or side pain, accompanied by fever or chills; nausea and vomiting (severe); painful or difficult urination, accompanied by fever or chills; stomach cramps
- **Rare**
  - Blood in urine or stools; pinpoint red spots on skin; unusual bleeding or bruising

Check with your health care professional as soon as possible if any of the following side effects occur:

- **Rare**
  - Chest pain; cough; shortness of breath; tingling of hands and feet, followed by pain, redness, and swelling; trouble with balance

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

- **More common**
  - Loss of appetite; nausea and vomiting; skin rash and itching; weakness
- **Less common**
  - Dry or cracked skin

This medicine often causes a temporary loss of hair. After treatment with fluorouracil has ended, normal hair growth should return.

After you stop receiving fluorouracil, it may still produce some side effects that need attention. During this period of time, *check with your doctor or nurse immediately* if you notice any of the following:

- Black, tarry stools; blood in urine or stools; cough or hoarseness, accompanied by fever or chills; fever or chills; lower back or side pain, accompanied by fever or chills; painful or difficult urination, accompanied by fever or chills; pinpoint red spots on skin; unusual bleeding or bruising

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your health care professional.

## Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, fluorouracil is used in certain patients with the following medical conditions:

- Cancer of the outside layer of the adrenal gland
- Cancer of the anus
- Cancer of the bladder
- Cancer of the cervix
- Cancer of the endometrium
- Cancer of the ovaries

- Cancer of the esophagus
- Cancer of the head and neck
- Cancer of the penis
- Cancer of the liver
- Cancer of the prostate
- Cancer of the skin
- Cancer of the vulva
- Carcinoid tumors
- Hepatoblastoma (a certain type of liver cancer that occurs in children)
- Glaucoma, during and after certain surgery (trabeculectomy)

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 05/04/2001

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## Drug Information: Methotrexate For Cancer (Systemic)

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202355.html>

### Brand Names

In the U.S.—

In Canada—

Another commonly used name is amethopterin.

### Category

- Antineoplastic

### Description

Methotrexate (meth-o-TREX-ate) belongs to the group of medicines known as antimetabolites. It is used to treat cancer of the breast, head and neck, lung, blood, bone, and lymph, and tumors in the uterus. It may also be used to treat other kinds of cancer, as determined by your doctor.

Methotrexate blocks an enzyme needed by the cell to live. This interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by methotrexate, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with methotrexate, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Methotrexate is available only with your doctor's prescription, in the following dosage forms:

#### *Oral*

- Tablets (U.S. and Canada)

#### *Parenteral*

- Injection (U.S. and Canada)

### Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

- Back pain; cough or hoarseness accompanied by fever or chills; dark urine; dizziness; drowsiness; fever or chills; headache; lower back or side pain accompanied by fever or chills; painful or difficult urination accompanied by fever or chills; unusual tiredness or weakness; yellow eyes or skin

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

- *More common*
  - Loss of appetite; nausea or vomiting
- *Less common*
  - Acne; boils; pale skin; skin rash or itching

This medicine may cause a temporary loss of hair in some people. After treatment with methotrexate has ended, normal hair growth should return.

After you stop using methotrexate, it may still produce some side effects that need attention. During this period of time, check with your doctor as soon as possible if you notice any of the following side effects:

- Back pain; blurred vision; confusion; convulsions (seizures); dizziness; drowsiness; fever; headache; unusual tiredness or weakness

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

## Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, methotrexate is used in certain patients with the following medical conditions:

- Acute nonlymphocytic leukemia (a type of cancer of the blood and lymph system)
- Cancer in the membranes that cover and protect the brain and spinal cord (the meninges)
- Cancer of the bladder
- Cancer of the brain (lymphoma)
- Cancer of the cervix
- Cancer of colon and rectum
- Cancer of the esophagus
- Cancer of the ovaries
- Cancer of the pancreas
- Cancer of the penis
- Cancers of the soft tissues of the body, including the muscles, connective tissues (tendons), vessels that carry blood or lymph, or fat
- Cancer of the stomach
- Hodgkin's lymphoma (a cancer of the lymph system, a part of the body's immune system)

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 08/01/2000

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## Drug Information: Cytarabine

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682222.html>

(sye tare' a been)

Brand name(s): Cytosar-U

Other name(s): Ara-C; Cytosine arabinoside

### IMPORTANT WARNING:

Cytarabine can cause a decrease in the number of blood cells in your bone marrow. Your doctor will order tests before, during, and after your treatment to see if your blood cells are affected by this drug.

### About your treatment

Your doctor has ordered the drug cytarabine to help treat your illness. The drug can be given by injection into a vein or under the skin of your forearm. In special situations, it may be injected into the spinal cord.

This medication is used to treat:

- certain types of leukemias

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Cytarabine belongs to a group of drugs known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up cytarabine, which then interferes with their growth.

### Other uses for this medicine

Cytarabine also is used to treat non-Hodgkin's lymphoma. Talk to your doctor about the possible risks of using this drug for your condition.

### Precautions

Before taking cytarabine,

- tell your doctor and pharmacist if you are allergic to cytarabine or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially aminoglycoside antibiotics such as amikacin, gentamicin, netilmicin, and tobramycin; aspirin; digoxin (Lanoxin); flucytosine; and vitamins.
- tell your doctor if you have or have ever had kidney disease, liver disease, or gout.
- you should know that cytarabine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this drug. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable

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## Drug Information: Cytarabine®(Systemic)

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202177.html>

### Brand Names

#### In the U.S.—

- Cytosar-U

#### In Canada—

- Cytosar

Other commonly used names are ara-C; cytosine arabinoside.

### Category

- Antineoplastic

### Description

Cytarabine ( sye-TARE-a-been) belongs to the group of medicines called antimetabolites. It is used to treat some kinds of cancers of the blood. It may also be used to treat other kinds of cancer, as determined by your doctor.

Cytarabine interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by cytarabine, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with cytarabine, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Cytarabine is to be administered only by or under the immediate supervision of your doctor. It is available in the following dosage form:

#### *Parenteral*

- Injection (U.S. and Canada)

### Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

## Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, cytarabine is used in certain patients with the following medical conditions:

- Cancer of the lymph system
- Cancer of the brain and spinal cord

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 07/02/1998

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## Drug Information: Mercaptopurine

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682653.html>

(mer kap toe pyoor' een)

Brand name(s): Purinethol

Other name(s): 6-MP

### About your treatment

Your doctor has ordered the drug mercaptopurine to help treat your illness. The drug is taken by mouth in tablet form.

This medication is used to treat:

- leukemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Mercaptopurine belongs to a group of drugs known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up mercaptopurine which then interferes with their growth.

### Other uses for this medicine

Mercaptopurine also is used to treat many types of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, acute idiopathic polyneuritis, acute idiopathic nephrotic syndrome, psoriatic arthritis, erythroid aplasia, or myelofibrosis; idiopathic hemolytic anemia; macroglobulinemia; idiopathic thrombocytopenia purpura; idiopathic pulmonary hemosiderosis; multiple sclerosis; myasthenia gravis; uveitis; and ulcerative colitis. Talk to your doctor about the possible risks of using this drug for your condition.

### Precautions

Before taking mercaptopurine,

- tell your doctor and pharmacist if you are allergic to mercaptopurine or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially allopurinol (Zyloprim), anticoagulants ('blood thinners') such as warfarin (Coumadin), aspirin, and vitamins.
- you should know that mercaptopurine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this drug. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable method of birth control to prevent pregnancy. Mercaptopurine may harm the fetus.
- do not have any vaccinations (e.g., measles or flu shots) without talking to your doctor.

### Side effects

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## Drug Information: Thioguanine

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682099.html>

(thye oh gwah' neen)

Brand name(s): Tabloid

Other name(s): 6-TG, TG

### About your treatment

Your doctor has ordered the drug thioguanine to help treat your illness. The drug can be taken by mouth in tablet form.

This medication is used to treat:

- leukemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Thioguanine belongs to a class of medications known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up thioguanine, which then interferes with their growth.

### Precautions

Before taking thioguanine,

- tell your doctor and pharmacist if you are allergic to thioguanine or any other medications.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially aspirin, busulfan (Myleran), mesalamine (5-ASA, Asacol, Pentasa, Rowasa), olsalazine (Dipentum), sulfasalazine (Azulfidine), and vitamins.
- tell your doctor if you have or have ever had kidney or liver disease.
- you should know that thioguanine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this medication. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable method of birth control to prevent pregnancy. Thioguanine may harm the fetus.
- do not have any vaccinations (e.g., measles or flu shots) without talking to your doctor.

### Side effects

Side effects from thioguanine are common and include:

- headache
- weakness or achiness
- darkening of the skin
- loss of appetite or weight

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## Drug Information: Hydroxyurea

(Hydroxyurea brand name)

URL of this page: <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682004.html>

(hye drox ee yoor ee' a)

Brand name(s): Hydrea

### IMPORTANT WARNING:

Hydroxyurea may cause severe, life-threatening side effects, including certain cancers. Talk to your doctor about the risks of using hydroxyurea for your condition.

### About your treatment

Your doctor has ordered the drug hydroxyurea to help treat your illness. The drug in capsule form can be taken by mouth.

This medication is used to treat:

- melanoma
- chronic myelocytic leukemia
- ovarian cancer
- primary squamous cell carcinoma of the head and neck (excluding the lip)
- chronic myelogenous leukemia
- sickle cell anemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Hydroxyurea is in a class of drugs known as urea derivatives; it slows or stops the growth of cancer cells in your body. In sickle cell anemia, hydroxyurea decreases the episodes of painful crisis by decreasing the sickling of red blood cells. The length of treatment depends on the types of drugs you are taking, how well your body responds to them, and the type of cancer you have.

### Other uses for this medicine

Hydroxyurea also is used to treat polycythemia vera, psoriasis, hypereosinophilic syndrome, lung cancer, and a variety of other cancers. In addition, hydroxyurea has been used along with anti-infective and surgical therapy to treat chronic urinary tract infections caused by certain bacteria. Talk to your doctor about the possible risks of using this drug for your condition.

### Precautions

Before taking hydroxyurea,

- tell your doctor and pharmacist if you are allergic to hydroxyurea or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking,

**Table 1**

**Summary of kinds of cancer treated by antimetabolite chemotherapeutic products**  
(source: Medline Plus®)

**Fluorouracil**

Colon cancer

Rectum cancer

Breast cancer

Stomach cancer

Pancreas cancer

Others:

Cancer of the outside layer of the adrenal gland

Anus

Bladder

Cervix

Endometrium

Ovaries

Esophagus

Head and neck

Penis

Liver

Prostate

Skin

Vulva

Carcinoid tumors

Hepatoblastoma

**Methotrexate**

Cancer of the breast

Cancer of the head and neck

Lung cancer

Blood cancer

Bone cancer

Lymph cancer

Tumors in the uterus

Others:

Acute nonlymphocytic leukemia (cancer of the blood and lymph system)

Cancer of the Meninges

Bladder

Brain (lymphoma)

Cervix

Colon

Rectum

Esophagus

Ovaries

Pancreas

Penis

soft tissues of the body (muscles, connective tissue, vessels, fat)

Stomach

Hodgkin's lymphoma

**Cytarabine**

Cancers of the blood (leukemias)

Others:

Cancer of the lymph system

Cancer of the brain and spinal cord

**Mercaptopurine**

Leukemia

**Thioguanine**

Leukemia

**Hydroxycarbamide/Hydroxyurea**

Melanoma

Leukemia (chronic myelocytic leukemia and chronic myelogenous leukemia)

Cell carcinoma of the head, neck and cervix

Ovarian cancer

=====